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UPPER AGE LIMITS IN CLINICAL TRIALS: UNDER-REPRESENTATION OF THE ELDERLY POPULATION

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Abstract: The number of research studies and clinical trials conducted on the elderly (65+ years) has been increasing. There are growing concerns regarding age cutoffs as inclusion criteria in these studies. How old is too old to be a participant in a research study? If a clinical trial is studying the elderly population, should qualified, healthy participants be excluded simply because they are too old? Several recent reports have suggested that there is a lack of justification for setting upper age limits. Issues addressed in this paper include: (a) gender disparity, (b) comparison of "young-old" versus "old-old" subjects, (c) the external validity of extrapolating young results to old individuals, (d) the internal validity of subject mortality, and (e) verification of chronological age. Therefore, the purpose of this paper is to review the available data on ageism and make recommendations to rigorously justify or eliminate upper age cutoffs for studies examining the elderly based on the US Department of Health and Human Services (DHHS) and the US Food and Drug Administration (FDA) with safety and risk assessment in mind.

Key words: Elderly, clinical, ethics, ageism, drug trials, pharmaceutical.

In 2009, there were 39.6 million individuals 65 and older (12.9 % of the population). For 2010, this population number has increased to 40.3 million (13% of the population) (1, 2). It is projected that by year 2020, 2030, and 2050, the number of adults 65 and older will reach 55 million, 72.1 million, and 80 million, respectively (1, 2). As the elderly population grows, the demand for age-specific pharmaceuticals and nutritional supplements will also increase. Subsequently, the need for clinical research that studies this population's response to these products will rise. There have been hundreds of clinical trials conducted in the older adult population (>60 years), including those that study the effects of medications and treatments that the elderly may be using. However, due to the perception of safety issues, clinical trials are sometimes conducted on a younger population, and the results are extrapolated to older individuals (3-5). Because of the known age-related changes in human physiology, clinical trials in the elderly need to be conducted. Older adults will continue to educate themselves as the primary "consumers" of research, and they will make personal decisions based on the results of studies conducted with their peers. However, if older adults and elderly individuals should be participating inclinical trials, how old is "too old" to be a subject?

Several recent reports on the age-related inclusion and exclusion criteria for older adults in clinical trials have suggested that upper age limits are relatively arbitrary and unjustified. Yet, these age limits have been approved by ethics committees and institutional review boards (3, 5-9). For example, Bugeja et al. (10) reported that of 1,012 studies reviewed, 490 potentially included older individuals as subjects. Of those, 35% unjustifiably excluded elderly individuals, while 54% had no upper age limits. McMurdo et al. (11) re-evaluated the same search criteria as Bugeja et al. (10) and reported slightly better inclusion rates of elderly individuals, although 15% still excluded elderly patients. More recently, Bayer et al. (7) reviewed studies submitted to ethics committees to determine if an upper age limit was present, and if so, was it justified. Authors reported that only 2% (5 of 225 studies reviewed) had no upper age limit, while 90 studies (58%) limited the age of participants to within 45-100 years. The median upper age cut-off was 70 years. Furthermore, of 85 studies with an upper age limit, 46 were approved by the local ethics committee – 20 of which did not justify the upper age limit whatsoever. Similarly, Cruz-Jentoft and Gutierrez (2010) evaluated cohorts of approved studies in 1994, 1999, and 2004 where 36-40% were approved with an unjustified upper age limit. However, by 2007 this rate was down to 19% (8). Perhaps due to the perception that conducting research with elderly participants is unsafe, upper age

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limits to exclude the elderly from participating in clinical trials may be unjustified.

It has been argued that age should not be a barrier to inclusion when testing a pharmaceutical that might benefit an older population (3). Studies that have an age limit may risk reporting benefits (or a lack thereof) from the treatment in a misrepresented population (12). When analyzing the results of clinical trials with inferential statistics, misrepresenting the study population may limit the external validity of these trials. However, when attempts are made to broaden the study population, other issues become evident, such as gender disparity at older ages, the comparison of "young-old" and "old-old" adults, and subject mortality.

Foerch et al. (2010) reported gender disparity in studies including stroke patients with specific age limits, and the older the age cut-off, the greater proportion of women were represented (13), because men have a shorter life span than women (14). Thus, an upper age limit to ensure equal sample sizes between genders may be a logical justification for an upper age limit. Bowsher et al. (1993) has also emphasized that there are definitive differences between 65, 75 and 85 year old participants, and "young-old" and "old-old" subsamples should be equally represented (6). Talarico et al. (2004) reported that the incidence of cancer increases with age, while simultaneously, the enrollment and participation in clinical trials progressively decreases with age. Consequently, the disparity between study enrollment of cancer patients and overall incidence of cancer is increasing (15). Thus, placing upper age limits on clinical trials may result in a reduction of enrollment of older subjects that are more likely to benefit from the treatment due to age limits set. Finally, participant mortality and the negative impact on internal and external validity of the study (4, 5) may be problematic. Participant mortality is the loss of subjects from a clinical trial due to voluntary withdraw, adverse events, or even death. For instance, Engelter et al. (16) performed a systematic review evaluating studies that investigated intravenous thrombolysed stroke patients that were < 80 compared to > 80 years old. Although some studies had participants up to 97 years old, the incidence of participant mortality in people > 80 was three times greater (16). Performing the trials in a clinical or hospital setting may reduce the risk of subject mortality due to the integration of medical oversight and clinical research, which easing the concern that many investigators have. However, if a hospital is aware of and enrolling for clinical trials, many admitted patients are not eligible due to the upper age limits of the trial (17). Masoudi et al. (17) reviewed clinical trials with specific eligibility criteria and the primary diagnosis of heart failure. Individuals included in the studies were not representative of typical heart failure patients. Those included were mostly men, not of extreme ages, and had left ventricular dysfunction. The authors concluded that few older individuals with heart failure met the inclusion criteria for clinical trials and more research was recommended with a more representative population (17).

In addition to the aforementioned drawbacks of upper age limits, it is possible to encounter older adults who do not know their actual date of birth. When birth records do not exist, it is difficult or impossible to verify age. Moreover, some cultures define age by phases of life and not a chronological age (18). Another example of cultural differences in age is that Chinese adults may present their age according to the Chinese lunar calendar, which can add 1 to 2 years to the western definition of age based on the Gregorian solar calendar. In these instances, upper age limits in clinical trials are not only arbitrary, but impossible to abide by if the participant's age is within a few years of the cutoff.

Overall, elderly individuals are likely under-represented in clinical research due to the arbitrary and unjustified upper age limits that are often set as inclusion or exclusion criteria (3, 6-11, 13, 15, 19-21). Bugeja et al. (1997) suggested that even though elderly participants might be frail and more prone to comorbidities that might carry greater risks involved with participation, it is better to include them in a tightly-controlled clinical trial than for them to experiment on their own (10). Ageism, which is commonly defined as the discrimination against a particular age group, is difficult to justify – even though the elderly are often classified as a "special population." In the U.S., where the protection of human subjects is governed by the Department of Health and Human Services (DHHS), there are no specific regulations or additional protections for the elderly. According to the Institutional Review Board (IRB) Guidebook, "There is no age at which prospective subjects should become ineligible to participate in research," section H (22). However, there are additional risks with advancing age, and it is ultimately a decision for the ethics committee or IRB to determine if older participants may be exposed to more than minimal risks. Perhaps most convincingly, the U.S. Food and Drug Administration (FDA) suggests that the geriatric population should be utilized in clinical research without arbitrary age limits and that they should be represented sufficiently to allow comparison between young and older patients (23). Therefore, upper age limits as inclusion or exclusion criteria in research studies should be carefully considered and perhaps avoided unless logically justified.

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